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HAYES, R	
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), - days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-33 are pending in the application.
   Of the above, claims 6.21, 22-23 (AB species), 24.33 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-5, 22.23 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-33 were ~~are~~ subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-5, & 22-23, drawn to a purified mammalian protein, a polypeptide fragment, compositions, and agents that inhibit binding to the cytoplasmic domain of CD40 receptor, classified in Class 514; subclasses 2.

Group II. Claims 6-17 & 28, drawn to an isolated nucleic acid molecule, expression vector, a host vector system encoding CD40bp, and a method of producing the protein or polypeptide, classified in Class 435, subclass 69.1.

Group III. Claim 18-21, 22-23, 24-27, drawn to antibodies, agents that are anti-CD40 antibodies, antibody fragments, and hybridoma cell lines, classified in Class 435, subclass 240.27.

Group IV. Claim 29-31, drawn to a method of modulating cellular function by transfecting cells with nucleic acids encoding CD40 binding proteins, classified in Class 435, subclass 69.1. It should be noted that the current classification currently reflects the process steps of introducing a nucleic acid into a cell, transcribing and then translating it. No additional steps are stated toward modulating

a cellular function which may result upon amendment in the reclassification of this group.

Group V. Claim 32-33, drawn to a method for screening for a CD40 immunosuppressive agent, classified in Class 435, subclass 7.1.

Claims 22-23 link inventions I and III. In the event that Group I has been elected, claims 22-23 will be examined in regards to those embodiments related to a dominant inhibitory fragment of CD40bp, and not to those embodiments related to the anti-CD40 antibody which are in Group III.

Claim 29 is generic to a plurality of disclosed patentably distinct species comprising (A) the human CD40bp, or (B) an anti-CD40 antibody. Should the applicant elect this group in a continuing application, the applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. It should be noted that the species election of (A)the human CD40bp will result in claims 29 & 31 of Group IV being examined toward those embodiments, while election of (B) an anti-CD40 antibody will result in claims 29-30 of Group IV being examined to its embodiments. Because the separate classification of the protein species to Class 530/300 and the antibody species to Class 530/389.1+ also constitutes an extra burden on the examiner to search and consider the separable

groups, the requirement for a species election for examination purposes as indicated is proper.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

The inventions are distinct, each from the other because of the following reasons:

2. Although there are provisions under the section for "Relation of Inventions" in MPEP 806.05 for inventive groups that are directed to different products; restriction is deemed proper because these products appear to constitute patently distinct inventions for the following reason:

Groups I-III are directed to products that are physically and functionally distinct; protein, nucleic acid, and antibodies. Each of these products can be prepared by different processes, such as though chemical synthesis or isolation from natural sources using various isolation/purification procedures. For example, the binding protein of Group I is a fundamentally different molecule than the nucleic acid molecule of Group II, which in turn can be used to clone the protein, detect expression of the protein, or used as therapeutic agents in gene therapy.

The protein of Group I is a fundamentally different molecule than the antibody of Group III, which can be generated by immunizing animals with a small synthetic portion of the full length polypeptide. Although the antibody of Group III can be used in isolating the protein of Group I, the antibody can also be used diagnostically in other ways, such as in affinity chromatography or in immunoassays, or as a therapeutic agent. The protein can be utilized in making the antibody, but not visa versa. It is pointed out that there is a proper distinction between these groups, since each product is not required in order for the other to exist.

3. Although there are provisions under the section for "Relation of Inventions" in MPEP 806.05 for inventive groups that are directed to different methods; restriction is deemed proper because these methods appear to constitute patently distinct inventions for the following reason:

Groups IV-V are directed to methods to modulate cellular functions or to screen immunosuppressive agents for CD40 binding protein. Each of the methods require physically and functionally distinct elements and possess limitations. For example, the use of transfected cells in Group IV to express the CD40 binding protein or an anti-CD40 antibody are distinct from the use of the CD40 receptor protein to detect immunosuppressive agents as in

Group V; nor are receptor molecules required to be bound to a solid support for screening these agents as in Group V. These inventions are, therefore, patentably distinct, since one is not required for the other.

4. Inventions I & III *and* V are related as product *and* process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the binding protein of Group I and the antibodies of Group III can be used in other diagnostic or therapeutic methods, such as isolating related proteins by affinity chromatography, or used to detect problems with immunoglobulin expression, or used in any of the distinct inventions of Groups I & III as stated above; while the method of screening agents that can compete with CD40 binding protein can use constructs expressing various nucleic acids.

5. Inventions II *and* IV are related as product *and* process of use. The inventions can be shown to be distinct if either or both of the following can be shown as stated above (M.P.E.P. § 806.05(h)). In the instant case, the nucleic acids can be used

to encode the full length protein or antibody, detect expression of the protein or antibody, or used in gene therapy; while the method of modulating cellular function can use the protein itself, or antibodies specific to the CD40 binding protein.

6. Because these inventions are distinct for the reasons given above, they have acquired a separate status in the art as shown by their different classification, and a lack in the co-extensiveness of the search and examination for each group would constitute an undue burden on the examiner to search and consider all the separable groups, restriction for examination purposes as indicated is proper.

7. During a telephone conversation with Antoinette Konski on March 7, 1996, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-5 & 22-23 (the protein species). Affirmation of this election must be made by applicant in responding to this Office action.
Claims 6-21, 22-23 (the antibody species), 24-33 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Specification

8. The disclosure is objected to because of the following informalities: "disfunction" is misspelled (pg. 24, line 14); Fig. 4 "EE" is a typo (pg. 6, line 17); please check the remainder of the application for any other grammatical errors. Appropriate correction is required.

It should be noted that claim 22 was missing. Therefore, the numbering of claims is not accordance with 37 C.F.R. 1.126. Misnumbered claims 23-34 have been renumbered 22-33. Any future correspondences should refer to the new claim numbers.

Claim Rejections - 35 USC § 112

9. Claims 1-5, 22-23 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the human CD40 binding protein of SEQ ID NO 2. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification describes CD40 binding protein (CD40bp) as a protein putatively involved in the signal transduction of the CD40 receptor which bind to the cytoplasmic domain of the CD40 receptor. Claims 1-3 are rejected as being not commensurate in scope with the specification because the claims as currently recited encompass *any* mammalian protein having the ability to bind to *any* cytoplasmic region of any CD40 receptor, as well as any CD40bp fragment without setting forth any physical

characterization and little functional characteristics. By contrast, the specification is enabled only for human CD40bp with the *specific* amino acid sequence depicted in SEQ ID NO 2, because only this specific sequence has been disclosed to have the desired properties of the applicants' invention.

The name "mammalian protein", or a "polypeptide fragment", does not serve to sufficiently characterize and enable all of the proteins that are encompassed by the claims. Neither does a "human protein having a molecular weight of about 64 kD". The specification has not provided sufficient working examples or guidance to ensure that *all* fragments from all (64kD) proteins having the ability to bind to the cytoplasmic domain of CD40, as currently recited, are predictable for SEQ ID NO 2. Thus, the claims are not commensurate in scope with the specification, since the name of a protein is subject to change and, for example, many proteins can have the general structure illustrated in Figure 4C. Furthermore, the name encompasses proteins from different mammalian species, and the specification does not teach that the gene is conserved between *all* mammalian species. It is thus not predictable from the enabled human species of SEQ ID NO 2 that the skilled artisan would be able to make and/or isolate *any* CD40bp from *any* mammalian species the artisan chooses based on the teachings in the specification.

Truncating the amino acid sequence by one or more amino acids in order to make polypeptide fragments (as encompassed by claim 2) also is not commensurate in scope with the specification, since the specification does not disclose those residues that are critical for CD40bp's function, nor which residues can be altered and still maintain the desired functional activity of CD40bp. For example, *all* fragments of CD40bp could not be predicted to contain *any* or *all* of the desired properties of CD40bp, since no guidance is provided in the specification as to the minimal length or what amino acid residues are necessary for CD40bp's *specific* functional activity. As currently recited, polypeptide fragments can be any where from 2 amino acid to 566 amino acids long. The lack of guidance to these issues in the specification would not allow one of ordinary skill in the art to successfully predict what critical structural features of the protein are necessary for activity. Therefore, the skilled artisan could not determine without undue experimentation what alterations are tolerable in order to retain a functional invention, because of the vast number of possible embodiments that would need to be addressed in order to make and screen *all* possible relevant parameters for a functional protein.

For the above reasons, the specification does not enable all possible CD40 binding proteins or fragments, nor *all* agents that may have the ability to inhibit the binding of the mammalian CD40

specific protein to the cytoplasmic region of the CD40 receptor. Thus, the claims are not commensurate in scope with the specification but rather are broader than the supporting disclosure. Only those sequences specific to the CD40bp are enabled. For example, it is unknown what constitutes a dominant inhibitory fragment of CD40bp (as it relates to claims 22-23), since the specification provides no guidance to what parameters are required for possessing the properties of a dominant inhibitory fragment of CD40bp. The breadth of this claim is such that without any working models for *any* CD40 binding protein fragments or any other agents specific to the cytoplasmic domain of the CD40 receptor, the quantity of experimentation needed to isolate and characterize each of the above binding protein fragments would be unduly burdensome, since no guidance is provided in the specification on how to isolate *only* those fragments that would be predicted by the skilled artisan to still possess the desired "dominant inhibitory" properties of CD40-specific molecules. Amending these claims to reflect the *specific* amino acid molecule of SEQ. ID NO 2 should obviate the above rejections.

10. Claims 1-5, 22-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. It has been held that the recitation that an element "having the ability to" performing a function is not a positive limitation. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5 & 22 are rejected under 35 U.S.C. § 102(a) as being anticipated by Hu et al., Sato et al., *or* Mosialos et al.

Hu et al. teach the purification and sequencing of an approximately 64kD human CD40-binding protein (i.e., CD40bp; pg. 30070, 2nd column and paragraph, Figs. 2 and 4A, as it relates to a purified mammalian protein that binds the cytoplasmic region of CD40 receptor as recited in claims 1 & 3). Polypeptide fragments of CD40bp are disclosed in Figure 4B and 4E (as it relates to claim 2). Compositions comprising a (pharmaceutically) acceptable carrier (as it relates to claims 4-5) are met by the purified protein dissolved in H_2O or

PBS. The agent disclosed to inhibit the ability of the protein CD40bp to remain bound to the cytoplasmic domain of the CD40 receptor is PBS + 1% SDS + heat (pg. 30070, 1st column, 3rd paragraph; as it relates to claim 22).

Sato et al. teach the purification and sequencing of an approximately 62kD (i.e., within experimental error of approximately 64kD as it relates to claim 3) CD40-binding protein from human (i.e., mammalian CAP-1; pg. 117, 1st column and paragraph, Fig. 2). Polypeptide fragments of this protein are disclosed in the degradation fragments displayed below the 64kD band illustrated in Figure 2 (as it relates to claim 2). Compositions comprising a (pharmaceutically) acceptable carrier (as it relates to claims 4-5) are met by the purified protein dissolved in H_2O or PBS. The agent disclosed to inhibit the ability of the protein CAP-1 to remain bound to the cytoplasmic domain of the CD40 receptor is laemmli sample buffer + heat (pg. 114, top of 2nd column; as it relates to claim 22).

Mosialos et al. teach the purification and sequencing of an approximately 64kD human (i.e., mammalian) CD40-binding protein (i.e., LAP1; Figs. 1 and 5B, as it relates to claims 1 & 3). Polypeptide fragments of CD40bp are disclosed in Table 1 (and pg. 391, 2nd paragraph, as it relates to claim 2). Compositions comprising a (pharmaceutically) acceptable carrier (as it relates to claims 4-5) are met by the purified protein dissolved in H_2O

or PBS. The agent disclosed to inhibit the ability of the protein CD40bp to remain bound to the cytoplasmic domain of the CD40 receptor is SDS sample buffer + heat (pg. 396, 2nd column, 2nd paragraph; as it relates to claim 22).

12. Claims 1-5 & 22-23 are rejected under 35 U.S.C. § 102(a) as being anticipated by Cheng et al.

Cheng et al. teach the purification and sequencing of an approximately 64kD (i.e., 567aa X 110 daltons/aa) human CD40-binding protein (i.e., CRAF1; Fig. 1, identical to the CD40 binding proteins CD40bp of Hu et al. and LAP1 of Mosialos et al., pg. 1497, last paragraph, as it relates to a mammalian protein that binds the cytoplasmic region of CD40 receptor in claims 1 & 3). Polypeptide fragments of CRAF1 are disclosed in Figure 3 (as it relates to claim 2). Compositions comprising a (pharmaceutically) acceptable carrier (as it relates to claims 4-5) are met by the purified protein dissolved in H_2O or PBS. The agent disclosed to inhibit the ability of the protein CD40bp to remain bound to the cytoplasmic domain of the CD40 receptor is the C26-partial CD40 binding protein fragments (Fig. 3), that can act as a dominant negative (i.e., the equivalent of an inhibitory) protein that binds to the cytoplasmic domain of the CD40 receptor (pg. 1498, 1st column, last paragraph; as it relates to claims 22-23).

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Garnette Draper, can be reached on (703) 308-4232. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800

Robert C. Hayes, Ph.D.
March 21, 1996